Efficacy and safety of single-dose liposomal amphotericin B for visceral leishmaniasis in a rural public hospital in Bangladesh: a feasibility study

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Summary

Background To rapidly reduce the burden of visceral leishmaniasis for national elimination programmes, an acceptable, safe, and effective treatment is needed that can be delivered at primary health-care centres. We aimed to assess the tolerability, safety, and cure rate of single-dose liposomal amphotericin B (AmBisome, Gilead, USA) for visceral leishmaniasis treatment in such a setting in Bangladesh.

Methods We enrolled patients who had been diagnosed with visceral leishmaniasis at Muktagacha upazila (subdistrict) hospital, Bangladesh. Eligible participants were at least 5 years old and had a history of fever for more than 2 weeks, splenomegaly, rK39 rapid test positivity, and haemoglobin concentrations of at least 50 g/L. Participants were provided a one-off intravenous infusion of liposomal amphotericin B (10 mg/kg bodyweight). Clinical assessments were done during treatment, before hospital discharge, and on days 30 and 180 after treatment. Cure was defined as resolution of fever, decrease in spleen size, and an increase in haemoglobin by 10% compared with baseline or to at least 100 g/L. We estimated efficacy in terms of initial cure (at day 30) and final cure (at 6 months), and safety in all patients who were enrolled (intention-to-treat analysis). We also assessed efficacy in all patients who completed treatment and 6 month follow-up after treatment with or without visceral leishmaniasis relapse (per protocol analysis). We assessed acceptability in terms of proportion of patients who consented to treatment. This study was registered with the Australian New Zealand Clinical Trial Registry, number CTRN12612000367842.

Findings Between March 5, and Aug 14, 2012, 329 (55%) of 594 cases of suspected visceral leishmaniasis were confirmed. Of these cases, five patients did not consent to treatment and 24 were ineligible for treatment. In the intention-to-treat analysis, 261 (87%) of 300 patients achieved initial cure and 290 (97%) achieved final cure. In the per-protocol analysis, 260 (88%) of 296 patients achieved initial cure and 289 (98%) achieved final cure. One patient did not start treatment owing to an allergic reaction to liposomal amphotericin B. During treatment or within 2 h afterwards, 79 (26%) patients developed fever, 109 (36%) had fever with rigor, and 56 (19%) had hypotension. No patients needed referral to a tertiary hospital for management of adverse events.

Interpretation Treatment of visceral leishmaniasis in a primary health-care facility with single-dose liposomal amphotericin B could safely and effectively be adopted by the national visceral leishmaniasis elimination programme in Bangladesh.

Funding Neglected Tropical Diseases (WHO), Agencia Española de Cooperación Internacional.

Introduction

Visceral leishmaniasis is potentially fatal, and causes substantial morbidity in 200 000–400 000 individuals every year, of whom 90% live in the Indian subcontinent. Visceral leishmaniasis causes extreme suffering and financial loss in the poorest populations, who mostly live in remote rural areas. The greatest burden falls on India, with more than 100 000 new cases every year, and Bangladesh, with an estimated 12 440–24 900 new cases per year.[1]

In 2005, the Governments of Bangladesh, India, and Nepal committed to eliminate visceral leishmaniasis by 2015.[2] The elimination strategy included the prompt treatment of cases with oral miltefosine. This drug was the only realistic option at the time, despite its potential teratogenicity, risk of non-compliance, and propensity for development of resistant strains.[3] However, after rollout, miltefosine showed an effectiveness of only 83% in a phase 4 trial in Bangladesh, and in Nepal 20% of study participants relapsed after 12 months with a final cure rate of only 79%.[4,5] These limitations, and the restrictions in the use of miltefosine (it is contraindicated in pregnancy and caution must be taken in women of childbearing age), restricts its use in large-scale programmes.

Short-course combination therapy regimens as alternatives to miltefosine—including liposomal amphotericin B plus miltefosine, paromomycin, or miltefosine plus paromomycin—showed promising results in a phase 3 trial in India, but the results of the

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implementation studies at the primary health-care level will only be available in 2015.[6,7] The only other option is liposomal amphotericin B (AmBisome, Gilead, USA), which has been shown to be very effective and safe for treatment of visceral leishmaniasis.[8] Previously, the liposomal form was prohibitively expensive for use in control programmes, but, in 2007, Gilead announced a price reduction of 90% (US$18 per 50 mg vial) for all low-income and middle-income countries in which visceral leishmaniasis is endemic. The reduction in price opened up the possibility of use of liposomal amphotericin B in these resource-poor settings. A phase 3 study[9] in India showed an efficacy of 95·7% with a single-dose regimen of liposomal amphotericin B at a dose of 10 mg/kg, with only minor side-effects. However, this study did not report rates of hypersensitivity. This result led to the recent recommendation of the WHO Expert Committee on the Control of Leishmaniasis to use liposomal amphotericin B as a first-line treatment for visceral leishmaniasis in the Indian subcontinent.[10]

Immediate rollout of an effective and safe short-course treatment regimen is essential for the attack phase of the visceral leishmaniasis elimination programme, which aims to reduce the incidence to less than one case per 10 000 population at risk.[11] A single-dose liposomal amphotericin B regimen, which is very effective, safe, and is likely to have fewer issues of poor compliance because of its lower side-effect profile, is in principle an ideal alternative to miltefosine. However, distribution of liposomal amphotericin B requires a cool chain, which might be an impediment to its implementation in remote regions where most of the visceral leishmaniasis patients seek care. Therefore, studies into the feasibility of the use of liposomal amphotericin B in rural public hospitals are needed.

In this study, we aimed to assess the effectiveness, safety, and feasibility of a 10 mg/kg single-dose liposomal amphotericin B regimen in a rural public hospital in Bangladesh. Results will not only serve the national visceral leishmaniasis control programme of Bangladesh, but will also allow the regional elimination programme to make an informed decision on changing its large-scale treatment strategy.

Methods

Study design and participants

The study was done in the Muktagacha upazila hospital (subdistrict hospital) of the district of Mymensingh, which is one of the areas of Bangladesh where visceral leishmaniasis is most endemic. We enrolled participants of either sex, who were aged at least 5 years, and had a history of fever for more than 2 weeks, splenomegaly, rK39 rapid test positivity, and haemoglobin concentrations of at least 50 g/L.

We excluded participants with a history of intercurrent or presence of clinical signs or symptoms of uncontrolled concurrent diseases or conditions before start of study treatment, any condition that might prevent the patient from completing the study therapy and subsequent follow-up (investigator assessed), a history of allergy or hypersensitivity to amphotericin B, previous treatment for visceral leishmaniasis within 2 months of enrolment, previous treatment failure with amphotericin B, post-kala-azar dermal leishmaniasis, and pregnant women. We excluded pregnant women from this study because present evidence about safety of liposomal amphotercin B during pregnancy is limited. Furthermore, visceral leishmaniasis during pregnancy needs to be managed in the tertiary hospital even with liposomal amphotericin B. Only participants who provided informed written consent to participate in the study were enrolled. The study was approved by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), and WHO's ethics committee.

Procedures

Before study start, two training sessions in management of liposomal amphotericin B and treatment of patients with visceral leishmaniasis with liposomal amphotericin B were given to the hospital staff of Muktagacha (by SS). Refresher training was provided by DM.

At enrolment, we took a complete medical history, did a physical examination, and measured bodyweight (with a Salter scale 465; Salter, Australia), height (with a locally made height scale), and haemoglobin concentrations (with the HemoCue system; HemoCue, Kuvettgatan, Sweden), and did a second rK39 test (with kala-azar detect; InBios, Seattle, WA, USA). We did a urine-based test for pregnancy for female patients of childbearing age.

All participants were admitted to the kala-azar ward of Muktagacha hospital for 1 night and followed up during this time by the hospital's doctor and nurse. All participants received paracetamol (500 mg for adults and 10 mg/kg for children younger than 12 years) and chlorphenamine (4 mg for adults and 1–2 mg for children younger than 12 years). We tested for potential allergies to study drug before the main infusion, consisting of 1 mg of liposomal amphotericin B diluted in 12·5 mL of dextrose 5% in water and administered for about 15–20 min.

Participants who did not show any allergic reaction during the allergic test received a dose of 10 mg/kg of liposomal amphotericin B. The intravenous infusion was administered over 2 h. Vital parameters were taken before trial medication, every 30 min during the drug infusion, 2 h and 24 h after treatment, and before discharging of the patient. We measured haemoglobin concentrations before treatment, before discharge from hospital, on day 30, and on day 180 after treatment.

After completion of physical examinations, participants were discharged from the hospital about 24 h after the infusion. Patients were requested to return for a follow-up visit at 30 days and 180 days after treatment. They were also instructed to visit the hospital if they did not

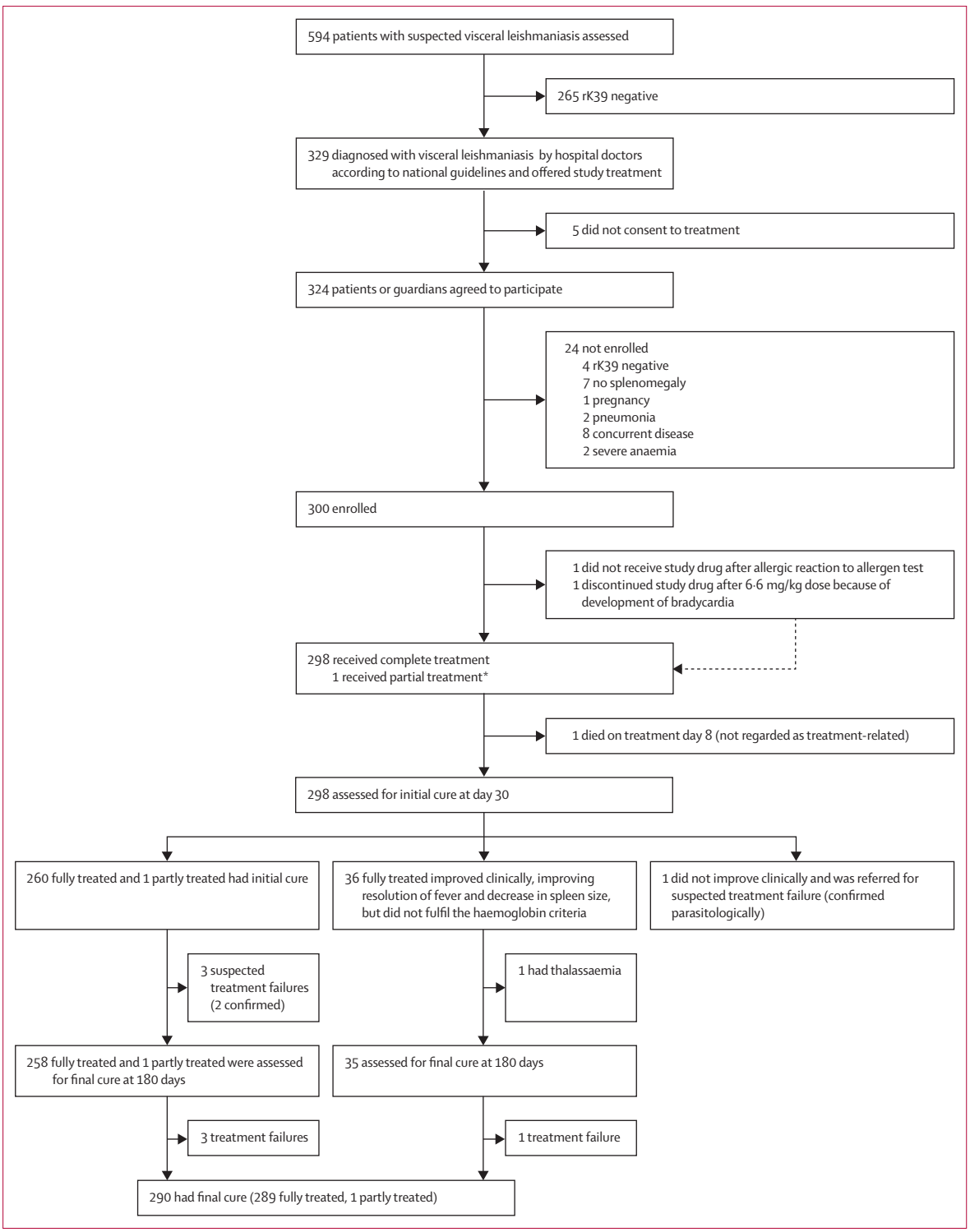

Figure: **Study profile**
*Patient with bradycardia received partial treatment.

feel well at any time during follow-up. At the follow-up visits, patients underwent full clinical examination and had a haemoglobin concentration test. Patients with suspected treatment failure or relapse of visceral leishmaniasis were referred to Muktagacha hospital where, after clinical assessment by the hospital doctors,

they were referred to a specialised visceral leishmaniasis hospital (Surja Kanta Kala-azar Reseach Centre) of Mymensingh Medicial College Hospital for parasitological confirmation and management. Patients who were referred to the specialised centre because of initial failure of treatment as defined by study criteria, but did not require rescue treatment following their assessment by visceral leishmaniasis experts, were also followed up for final cure.

At day 30 after treatment we assessed rates of initial cure, which was defined as resolution of fever, decrease in spleen size, and an increase in haemoglobin concentration by 10% compared with baseline or to at least 100 g/L. Participants who were deemed to have initial cure, were followed up for 6 months for assessment of final cure, defined as the absence of relapses after day 30, decrease in spleen size compared with day 30, and increase of haemoglobin by 10% compared with day 30 or to at least 100 g/L. Treatment failure was assumed if a patient did not achieve initial cure and had *Leishmania donovani* amastigotes in their spleen aspirate. A patient with initial cure, but with reappearance of visceral leishmaniasis symptoms during follow-up and *L donovani* bodies in their spleen aspirate was defined as a case of visceral leishmaniasis relapse. All participants with parasitologically confirmed treatment failure or relapse received rescue treatment with liposomal amphotericin B at total dose of 15 mg/kg bodyweight (three injections of 5 mg/kg each over 3 days) in the specialist centre in Mymensingh.

Statistical analysis

The main objective of this study was to obtain data for feasibility of use of single-dose liposomal amphotericin B at the peripheral level close to the endemic villages. A purposive sample size was determined, assuming that at least 85% of patients with visceral leishmaniasis who attended the hospital were eligible to be treated with single-dose liposomal amphotericin B, and aiming to obtain at least 95% cure rate at 6 months and with up to 3% of treated patients developing drug-related adverse events requiring referral to a tertiary hospital for management. Data are expressed as mean values. We calculated cure rates in the intention-to-treat population (all patients who received at least one dose of study drug) and per-protocol population (patients who received complete dose of 10 mg/kg and were followed up for

	Children aged <18 years (n=175)	Adults aged ≥18 years (n=125)	Overall (n=300)
Age, years			
Mean (SD)	9·4 (3·1)	32·5 (10·9)	19 (13·61)
Median (IQR)	9 (7–11)	30 (22·5–42)	13 (8–27)
Sex			
Female	68 (39%)	43 (34%)	111 (37%)
Male	107 (61%)	82 (66%)	189 (63%)
Primary visceral leishmaniasis	132 (75%)	100 (80%)	232 (77%)
Previous treatment for visceral leishmaniasis	43 (25%)	25 (20%)	68 (23%)
Miltefosine monotherapy	34 (19%)	12 (10%)	46 (15%)
Paromomycin monotherapy	1 (1%)	5 (4%)	6 (2%)
Sodium stibogluconate	4 (2%)	6 (5%)	10 (3%)
Multidose liposomal amphotericin B	4 (2%)	2 (2%)	6 (2%)
Mean patient-reported duration of fever, days	68·1 (38·2)	63·4 (39·8)	66·2 (38·9)
Spleen size at enrolment, cm			
Mean (SD)	6·9 (3·7)	6·4 (3·7)	6·6 (3·7)
≤5	82 (47%)	46 (37%)	128 (43%)
5–<10	74 (42%)	59 (47%)	133 (44%)
≥10	19 (11%)	20 (16%)	39 (13%)
Mean (SD) bodyweight at baseline, kg	22·4 (9·7)	44·0 (6·8)	31·4 (13·7)
Mean (SD) BMI at baseline, kg/m²	13·7 (1·8)	17·5 (2·0)	15·3 (2·6)
Underweight*	126 (72%)	92 (74%)	218 (73%)
Systolic/diastolic blood pressure, mm Hg	100/65 (80/50–120/90)	104/67 (80/50–120/90)	102/66 (80/50–120/90)
Pulse rate, beats per min	97·4 (66–128)	85·5 (60–120)	92·4 (60–128)
Respiratory rate, breaths per min	24·1 (16–40)	21·7 (16–32)	23·1 (16–40)
Body temperature, °C	37·0 (35·5–39·9)	37·0 (36–40)	37·0 (35·5–40·0)
Haemoglobin, g/L	9·3 (5·1–14·4)	9·9 (5·1–16·4)	9·6 (5·1–16·4)

Data are n (%) or mean (range), unless otherwise stated. BMI=body-mass index. *BMI during enrolment of <18·5 kg/m² for adults and BMI <5th percentile for children according to the US Centers for Disease Control and Prevention BMI Percentile Calculator for Children and Teens.

Table 1: **Baseline characteristics**

6 months after treatment). Safety analysis included calculation of incidence of all adverse events. We compared cure rates between different age groups and with disease types (primary *vs* relapse) with the χ^2 test and Yate's correction where applicable. We regarded $p \leq 0 \cdot 05$ as significant.

This study was registered with the Australian New Zealand Clinical Trial Registry, number CTRN12612000367842.

Role of funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 300 participants between March 5 and Aug 14, 2012, and 6 month follow-up was completed by Feb 14, 2013 (figure, table 1). Notably, 232 (77%) of participants had primary visceral leishmaniasis and 68 (23%) were relapses. 46 (68%) of these patients with relapse had previously received miltefosine. In general, study patients were underweight and young (table 1). 175 (58%) patients had anaemia, defined as a haemoglobin concentration of less than 100 g/L.

One adult developed hypotension during the allergy test with 1 mg amphotericin B and did not begin treatment because of concern over hypertensive shock, and was treated with oral miltefosine. Study drug infusion was stopped in another participant after 1 h because of prolonged bradycardia. These problems were locally managed and reverted without consequences. Thus 298 participants completed the full treatment, and one patient had completed partial treatment. Mean dose of amphotericin B was 313·87 mg (range 110–660), with a mean volume of amphotericin B of 78·47 mL (27·50–165·0) and diluents of 234·40 mL (82·5–495·0). One male patient aged 39 years died on day 8 after treatment because of an exacerbation of a pre-existing chronic obstructive pulmonary problem that was not related to the study drug. Therefore, 298 participants were available for assessment of initial cure at day 30.

Table 2 shows initial cure rates in the intention-to-treat and per-protocol populations. One participant did not show any clinical improvement and was referred to the specialist centre, where a spleen aspiration confirmed the presence of leishmania parasites. The remaining 36 participants who were not regarded as initially cured according to the study protocol had not reached the necessary increase in haemoglobin concentrations by 10% compared with baseline value. However, these 36 participants had no clinical evidence of active diseases. In all these patients, spleen sizes had decreased in size and no recurrence of fever was noted. Nevertheless, we referred them to the hospital doctor. On the basis of hospital doctor's judgment, they were not referred to the specialist hospital, but were followed up closely and their haemoglobin concentration was assessed on day 60 or day 90. In all cases apart from one, the haemoglobin concentration increased to more than 100 g/L at day 60 or day 90, and therefore these patients were asked to return for final cure assessment. One patient was diagnosed with thalassaemia at the specialist centre (figure).

No participants were lost during the follow-up period. Between day 30 and day 180 assessment, seven participants relapsed, resulting in a per-protocol final cure rate at 6 months of 98% and an intention-to-treat cure rate of 97% (table 2).

Most patients tolerated single-dose liposomal amphotericin B (table 3). All drug-related adverse events were mild-to-moderate and all were managed with the resources available at the Mugtagasha upazila hospital. None of the participants required referral to tertiary hospital for complications. The most common adverse event during trial medication was fever, vomiting, and fever with rigor (table 3). Within 2 h of medication, the most common adverse event was fever with rigor followed by fever and hypotension (table 3), which responded well to oral rehydration therapy only. On the day after infusion, all patients were afebrile and all adverse events had resolved.

We noted a reduction in haemoglobin concentrations of 2·00–2·75 g/L in six (2%) of 299 participants, without

	Intention-to-treat analysis		Per-protocol analysis*	
	n/N (%)	Difference (95% CI; p value)	n/N (%)	Difference (95% CI; p value)
Initial cure				
By age group		9·3% (1·2–17·3; 0·075)		8·6%(1·0–16·5; 0·041)
Children	159/175 (91%)		159/174 (91%)	
Adult	102†/125 (82%)		101/122 (83%)	
By visceral leishmaniasis type		9·2% (2·0–16·5; 0·075)		8·0% (1·0–15·2; 0·121)
Primary	197†/232 (85%)		197/229 (86%)	
Relapse	64/68 (94%)		63/67 (94%)	
Overall	261†/300 (87%)		260/296 (88%)	
Final cure				
By age group		1·6% (–2·4–5·6; 0·664)		2·6% (–1·5–5·7; 0·282)
Children	168/175 (96%)		168/174 (97%)	
Adult	122†/125 (98%)		121/122 (99%)	
By visceral leishmaniasis type		4·3% (1·7–6·9; 0·175)		3·1% (1·0–5·3; 0·322)
Primary	222†/232 (96%)		222/229 (97%)	
Relapse	68/68 (100%)		67/67 (100%)	
Overall	290†/300 (97%)		289/296 (98%)	

*Four patients were excluded; one patient was lost to follow-up because of a serious adverse events not regarded as related to study drug; one patient had a partial treatment; one patient was misdiagnosed; and one patient was hypersensitive to amphotericin B. †One patient with partial treatment achieved initial and final cure.

Table 2: **Efficacy of single-dose liposomal amphotericin B for visceral leishmaniasis**

any clinical signs or symptoms associated with the reduction. Four female participants became pregnant within months after treatment and in one the pregnancy was completed with delivery of a term normal birth after 6 months of follow-up. The other three pregnant women were clinically healthy during the last follow-up visit.

	Events during treatment	Events within 2 h after treatment
Fever	36 (12%)	43 (14%)
Fever with rigor	22 (7%)	87 (29%)
Hypotension	19 (6%)	37 (12%)
Hypothermia	4 (1%)	9 (3%)
Nausea	4 (1%)	4 (1%)
Vomiting	32 (11%)	3 (1%)
One time	27 (9%)	1 (<1%)
Two times	2 (1%)	1 (<1%)
Three times	3 (1%)	0
Four times	0	1 (<1%)
Headache	7 (2%)	2 (1%)
Epigastria, abdominal pain, or abdominal discomfort	3 (1%)	0
Mild skin allergic rash*	3 (1%)	0
Back pain	1 (<1%)	1 (<1%)
Neck ache	1 (<1%)	0
Body ache	2 (1%)	0
Bradycardia†	1 (<1%)	0
Diarrhoea	0	2 (1%)
Restlessness	1 (<1%)	0

*Managed by antihistamines (in three patients) and hydrocortisone treatment (in one patient). †Managed with 0·6 mg intramuscular atropine.

Table 3: **Safety profile for all 300 enrolled patients**

Panel: Research in context

Systematic review

In 2010, the WHO Expert Advisory panel on leishmaniasis recommended intravenous single infusion with liposomal amphotericin B (10 mg/kg bodyweight) for treatment of visceral leishmaniasis in the Indian subcontinent to quickly reduce cases of the disease. To investigate the basis of this recommendation, we searched PubMed for articles published in English with the search terms "visceral leishmaniasis", "treatment", "liposomal amphotericin B", and "single dose". We identified four randomised controlled trials with single doses of liposomal amphotericin B, ranging from 5 mg/kg to 15 mg/kg doses. Three of these four studies were done in India by one group. The only study with a 10 mg/kg single dose was fairly small. These studies showed a high efficacy and safety profile when given to patients with visceral leishmaniasis in controlled conditions. However, little information existed about the feasibility, acceptability, cure rates, and safety profile of single-dose liposomal amphotericin B for visceral leishmaniasis if given in uncontrolled condition such as in a rural primary care hospital (where most of the cases with visceral leishmaniasis seek medical care).

Interpretation

The feasibility of single-dose liposomal amphotericin B we noted at the community level will help inform policy makers. On the basis of our study and previous trials, single-dose liposomal amphotericin B should be the front-line treatment for visceral leishmaniasis in Bangladesh and neighbouring countries. The clinical implications are important, because patients can now be diagnosed and cured of visceral leishmaniasis in 1 day in a rural hospital setting, which will greatly improve compliance, and with high efficacy and low adverse events. Amphotericin B could therefore support the elimination of visceral leishmaniasis as a major public health problem in southeast Asia.

Discussion

In view of present treatment options, WHO has recommended monotherapy with liposomal amphotericin B during the attack phase of visceral leishmaniasis elimination to rapidly reduce the burden of the disease.[8,11] Therefore, our study provides an important assessment of the feasibility of administering single-dose liposomal amphotericin B close to endemic villages at a rural hospital primary health-care level (panel). Our study showed that treatment of visceral leishmaniasis was feasible in a rural hospital in Bangladesh with a single intravenous infusion of liposomal amphotericin B. Most patients were treated in the rural hospital only (91%), with a high acceptance (98%), cure rate (97% in the intention-to-treat analysis), and good safety profile. We noted no serious adverse events related to study drug and all adverse events were manageable in the hospital with straightforward procedures. Thus, we believe single-dose liposomal amphotericin B offers the best option in terms of efficacy and compliance during the attack phase of the visceral leishmaniasis elimination programme and this strategy could be extended to Bangladesh, India, and Nepal.

Furthermore, a study in the five most visceral leishmaniasis endemic upazilas (subdistricts) in Mymensingh district noted that implementation of one-off intravenous infusion of liposomal amphotericin B was technically and operationally feasible (Eva-Maria Maintz [Freiburg University, Freiburg, Germany]; unpublished data). In that study, most of the consumables needed for drug preparation and administration were available, all hospitals were equipped with a generator for periods when the central electricity supply was cut due to loading issues, and most paramedic staff were familiar with intravenous infusion. The study noted that training was needed, but, as our study shows, this training was feasible in the Muktagacha district.

Before the start of the study, we expected referral of up to 3% visceral leishmaniasis cases to the tertiary hospital for management of eventual complications. However, no referral was necessary because all adverse events were mild. Incidence of adverse events was about 47% during treatment and 63% within 2 h after treatment and in all cases were manageable with simple intervention including oral rehydration solution for hypotension or vomiting and antipyretics for fever and rigor. Furthermore, four pregnancies occurred after of treatment during the follow-up period. Pagliano and colleagues noted in their observational study[12] that liposomal amphotericin B for visceral leishmaniasis during pregnancy was safe and effective for mother and fetus. Firm conclusions about safety and efficacy during pregnancy and for the fetus cannot be made on the basis

of our study, but our findings are encouraging and a long-term follow-up is planned.

Despite the good safety profile we noted, some concerns emerged. One patient (<1%) had hypersensitivity to liposomal amphotericin B. Thus, the allergic test needs to be done as recommended by the manufacturer (ie, allergic test with 1 mg liposomal amphotericin B) and should not be done with the prepared solution for intravenous infusion. This strategy will help to avoid wastage and will ease management of the patient if they are allergic to the drug. In another patient (<1%), treatment had to be interrupted because of development of bradycardia. We noted haemoglobin reductions in six treated patients (2%), warranting close follow-up of patients during treatment and within 24 h after treatment for eventual drug-related cardiac toxicity and potential cardiac failure from significant reductions of haemoglobin concentration.

56 (19%) patients with visceral leishmaniasis were hypotensive. Medical staff should therefore be prepared for its management before the start of treatment. Haemoglobin concentrations were a good indicator of cure and concentrations did not reach normal for more than a month in a small proportion of participants. However, our study showed that low initial haemoglobin concentrations are not associated with a failure of treatment.

A potential question for implementation of liposomal amphotericin B is the risk of resistance. However, when used as a single dose, the risk of resistance is very low. Lachaud and colleagues showed no emergence of leishmania resistance to liposomal amphotericin B even after repeated multidose treatments or single-dose prophylaxis use in immunosuppressed patients with visceral leishmaniasis.[13] Also, no guarantee exists that any treatment combination is safe from resistance: resistance to combinations can be selected for in vitro over long periods.[14,15] We suggest that combination therapies could be considered once the elimination target has been reached with single-dose liposomal amphotericin B.

Overall, treatment of visceral leishmaniasis with single-dose liposomal amphotericin B in a rural hospital in Bangladesh was feasible, acceptable, safe, and efficacious. The present recommendation of WHO for its use as a first-line drug for visceral leishmaniasis in southeast Asia is supported by these results. The national visceral leishmaniasis elimination programme in Bangladesh should consider its implementation in practice and such a strategy could represent an example for India and Nepal, especially when combined with active case detection and vector control.

Contributors

The authors accept full responsibility for the content of the report. DM, JA, SGN, SS, GM, and BA designed the study. SS did the training. DM was the principal investigator, MGH and SGN were coprincipal investigators, and JA, GM, and BA were study coordinators. MGH, DG and MSH enrolled and managed patients and collected clinical data. DM and SGN monitored field activities and clinical data collection. DM and MMH monitored data quality and analysed data. DM, BA, JA, GM, MGH, DG, and MSH participated in the writing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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